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EXAMINER	
HAMA, JOANNE	
ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/086,294	NIELSEN ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,9-22,25-40,78 and 79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,9-22,25-40,78 and 79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/28/02* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *see attached*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Application, filed February 28, 2002, is a continuation of U.S. Patent Application 09/024,932, filed February 17, 1998, now abandoned.

Claims 1, 3-5, 9-22, 25-40, 78, 79 are pending.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

The priority information on the signed declaration does not match the priority claimed in the first line of the specification.

Election/Restrictions

Applicant's election with traverse of Group IV (claims 3-5, 9-19, 21, 25-40, 78,79; claim 1 is a linking claim) in the reply filed on March 1, 2005 is acknowledged. The traversal is on the ground(s) that groups II, IV, and VI be grouped together, as there is no "serious burden on the examiner". The examiner has found the argument persuasive and will examine Groups II, IV, and VI.

It is noted that Groups I, III, and V have also been separated based on whether p53 protein were to be administered before, during, or after administration of a microtubule affecting agent. These Groups will be combined,

but will not be examined in this Office Action, as the Restriction separates p53 protein and a nucleic acid encoding p53. As a result of combining Groups II, IV, and VI, and Groups I, III, and V, the Groups and claims have been numbered, thus:

Group I: Claims 3-5, 18-22, 25-40, 78, 79, drawn to a method of treating mammalian cancer cells comprising contacting said cells with a p53 tumor suppressor protein and a microtubule affecting agent, classifiable in class 514, subclass 2.

Group II: claims 3-5, 9-22, 25-40, 78-79, drawn to a method of treating mammalian cancer cells comprising contacting said cells with a nucleic acid encoding p53 and a microtubule affecting agent, classifiable in class 514, subclass 44.

Claims 1, 3-5, 9-22, 25-40, 78, 79, drawn to a method of treating mammalian cancer cells deficient in functional p53, wherein the method comprises contacting cancer cells with a p53 tumor suppressor nucleic acid encoding p53, and also contacting said cells with a microtubule affecting agent, such that one or more disease characteristic of the cell is ameliorated, and wherein the mammalian cancer cells are human head and neck, ovarian, prostate, or mammary cancer cells, are under consideration.

Claim Objections

Claim 18 is objected to because of the following informalities: The use of the trademarks TAXOL® and TAXOTERE® has been noted in this application. It

should be capitalized wherever it appears and be accompanied by the generic terminology. Each letter of the mark should be capitalized (see MPEP 608.01(v)). TAXOTERE® needs to be capitalized in claim 18.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5, 9-22, 25-40, 78, 79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

1) an *in vitro* method of treating mammalian cancer cells deficient in functional p53, said method comprising contacting said cancer cells with a nucleic acid encoding p53 and also contacting said cancer cells with a microtubule affecting agent, such that one or more disease characteristic of the cancer cell is ameliorated, wherein the mammalian cancer cells are human head and neck, ovarian, prostate, or mammary cancer cells,

2) an *in vivo* method of treating mammalian cancer cells deficient in functional p53, said method comprising injecting intratumorally said cancer cells

with a nucleic acid encoding p53 and also contacting said cancer cells with a microtubule affecting agent, such that one or more disease characteristic of the cancer cell is ameliorated, wherein the mammalian cancer cells are human head and neck, ovarian, prostate or mammary cancer cells,

does not reasonably provide enablement for:

an *in vivo* method of treating mammalian cancer cells deficient in functional p53, said method comprising any route of administration of a nucleic acid encoding p53, other than intratumoral, to said cancer cells, and contacting said cancer cells with a microtubule affecting agent, such that one or more disease characteristic of the cancer cell is ameliorated, wherein the mammalian cancer cells are human head and neck, ovarian, prostate, or mammary cancer cells.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claimed invention is a method of treating mammalian cancer cells deficient in functional p53, wherein the method comprises contacting cancer cells with a p53 tumor suppressor nucleic acid encoding p53, and also contacting said cells with a microtubule affecting agent, such that one or more disease characteristic of the cell is ameliorated, and wherein the mammalian cancer cells are human head and neck, ovarian, prostate, or mammary cancer cells.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the

necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Claims 1, 3-5, 9-22, 25-40, 78, 79 are drawn to methods of treating cancer, hyperproliferative or metastatic cells using a tumor suppressor protein or nucliec acid and a microtubule affecting agent. Claims 1, 3-5, 9-22, 25-40, 78, 79 read broadly on treatment of any cancer, hyperproliferative, or metastatic cell in any environment (*in vitro, ex vivo,* or *in vivo*) from any organism. Further, claims 1, 3-5, 9-22, 25-40, 78, 79 read on any treatment with any tumor suppressor protein or nucleic acid, including an antisense molecule, and any microtubule affecting agent.

The specification, as filed, provides examples of methods wherein several cancer cell lines are treated *in vitro* (cell culture) with a combination of adenoviral delivered p53 and Taxol. Further, the specification presents examples of methods wherein immune compromised mice with implanted cancer cells, SK-OV-3, DU-145, MDA-MB-468, SCC-15, are treated with either a combination of adenoviral delivered p53 and Taxol, or a combination of adenoviral delivered p53, Taxol and cisplatin. However, the specification, as filed, des not provide guidance to an artisan to practice the full scope of the claimed invention.

The claims broadly encompass a method of treating wherein the nucleic acid vector is administered *in vivo*. While the specification at the time of filing teaches administration of an adenoviral vector administered to SCID mice via IP injection, the specification does not provide teachings that enable a skilled artisan to administer any DNA vector for the full scope of the claims. The art at the time of filing teaching that delivery of DNA constructs (i.e. gene therapy) was unpredictable. In the case wherein a mammal is administered a non-viral DNA construct, the specification teaches a skilled artisan that non-viral DNA vectors were known in the art (e.g. Casey, 1991, specification, page 67, line 19), neither the specification nor the art teach an artisan how to administer the non-viral DNA vector, such that the non-viral DNA vector could readily reach any cancer cell. While the art teaches several ways that non-viral DNA eukaryotic vectors could be introduced *in vivo* into cells, the art also teaches that there are many limitations when administering non-viral vectors. For example, Wolff et al. teach that some methods of directly introducing non-viral DNA vectors into the animal

include non-viral DNA encapsulated in liposomes. Non-viral DNA entrapped in proteoliposomes containing viral envelope receptor proteins, calcium phosphate-coprecipitated DNA, and DNA coupled to polylysine-glycoprotein carrier complex (Wolff, et al., 1990, Science, 247: 1465-1468; page 1465, 1st col., 1st parag., lines 11-18). Wolff et al. teach that non-viral DNA vectors can also be directly injected into muscle. However, the non-viral DNA vector, depending on its route of administration, only localizes to certain tissues or organs. As a result, the vector is not readily distributed throughout the body. For example, Wolff et al. show that the non-viral DNA is localized to the muscle at the site of injection (Wolff, et al., page 1465, 3rd col., 2nd parag.). Nicolau et al. demonstrated that non-viral DNA suspended in liposomes are localized to the liver and the spleen (Nicolau, et al., 1983, PNAS, USA, 80: 1068-1072; page 1068, 1st col., 1st parag.). Wolff et al. and Nicolau et al.'s studies demonstrate that an artisan cannot predict that injection of a non-viral DNA plasmid anywhere into an animal will reliably result in reduction of any tumor, in any part of the body. Another problem associated with using non-viral DNA vectors is that they suffer from inefficient gene transfer. Abdallah et al. (1995, Biol. Cell., 85: 1-7) teach that one of the major hurdles in using non-viral DNA *in vivo* is successfully having the vector enter the nucleus (Abdallah, et al., page 2, 1st col., 2nd parag.). In addition to this, expression from these non-viral vectors is transient (Somia and Verma, 2000, Nature Reviews, 1:91-99; page 91, 1st col., 2nd parag., lines 2-8)). While it may be that the instant invention could encompass using a non-viral vector comprising a nucleic acid sequence encoding p53 in the liver or muscle, and the time of expression

required to use the instant invention transient, the specification does not teach that these are the embodiments which are used to practice the invention. For that matter, the specification does not teach that a skilled artisan that the instant invention has certain limitations and can be used in certain applications. Rather, a skilled artisan would need to determine if long-term or short-term of gene expression is required for his/her study, determine whether or not the means of introducing a non-viral DNA expression vector is sufficient for duration of the study and determine if the transgene does reach the tumor, and determine whether the transgene is expressed at detectable levels. To determine these parameters require undue experimentation. In addition to these parameters, a skilled artisan needs to also consider the fact that gene transfer from non-viral vectors is unpredictable. In other words, it may not even be a salient system to use for gene expression. For reasons of unpredictability and undue experimentation, the specification has not enabled a skilled artisan to reliably obtain mammals treated with a non-viral transgene construct.

With regards using any viral vector as a vehicle to deliver a nucleic acid sequence encoding p53, the art teaches that viral vectors as a vehicle is unpredictable. These issues of unpredictability include immune responses to the transgene product, the dose of virus administer, the promoter chosen to drive expression of the recombinant gene, the innate immune mechanisms and direct cytotoxcity cause by expression of viral genes (see also Somia and Verma, page 92, Box 1). Additionally, some viral vectors (e.g. lentiviral/retroviral, adeno-associated viral) integrate into the host's genome. The integration into the host

genome is random, which then raises the issues as to whether the viral vector interrupted the function of another gene and whether the promoter used to drive expression of the transgene has now come under control of factors in the genome (e.g. enhancers). For these reasons, the use of a viral vector is determined empirically. However, the specification as filed does not provide sufficient guidance, working examples, and evidence as to how an artisan of skill would have made and used the claimed invention commensurate with the scope of the claims without undue experimentation.

The claims broadly encompass any nucleic acid encoding p53. This includes antisense. Antisense therapy treatments are highly unpredictable due to delivery issues and target accessibility (Branch, 1998, TIBS, 23: 45-50, see page 48, under "The three As of antisense-mediated gene ablation: access, access, and access"). In addition to delivery issues and target accessibility, Agrawal (1996, TIBTECH, 14:376-387) also teaches that design of an antisense molecule needs to be determined empirically. "A good part of nucleotide design for its target RNA varies significantly, depending on base composition and sequence. Therefore, the antisense activity of a selected oligonucleotide is influenced both by its base composition and by its sequence. Introduction of oligonuclotides that contain certain sequence motifs, such as CpG and GGGG (hyper-structure-forming sequences) induce cell proliferation and immune responses.... If an antisense oligonuclotide possess self-complementarity or a palindromic sequence, it can form stable secondary structures such as short linear duplexes or hairpins. In such cases, secondary structure formation

competes for binding to the target mRNA. In addition, these secondary structures can serve as decoys by binding to cellular factors, thereby inhibiting or inducing the functions of non-targeted genes, which could directly or indirectly alter the function of the gene being studied (page 377, second column, "Choice of oligonucleotide sequences," first and second paragraphs)." Thus, because not all antisense constructs will function as predicted, all antisense constructs need to be tested for function and efficacy. The specification does not provide any examples of antisense constructs that were able to reduce the expression level of a target gene and thus does not enable one skilled in the art to make and/or use a plasmid vector expressing therapeutic RNA in the treatment of an animal. Cell culture examples are usually not predictive of *in vivo* applications, and cannot address the issues involved with specific delivery to a target site *in vivo* in a whole organism. The specific embodiment disclosed by the applicant, wild-type p53 provided in combination with Taxol, is indicated as unpredictable in cell culture (Delia, et al. 1996, Nature Medicine, 2: 724-725, see IDS, filed March 11, 2004, page 724, 3rd col., last 8 lines to top of page 725), because "the cytotoxic response to Taxol is variably modulated by loss of wild-type function, possibly depending on the cell type and/or genetic background of the tumor cell." This would translate to further unpredictability of a positive therapeutic outcome *in vivo* (whole organism). Due to this unpredictability, *in vitro*, or even *in vivo*, results for one type of cancer, hyperproliferative, or metastaic cell would not correlate generally with any other cell type.

It is well known in the art that mouse models, particularly when immunosuppressed mice are used, do not always correlate with therapeutic results in humans or other organisms. "(M)ost drugs that work in lab animals tend to be duds in humans. The field is littered with "magic bullets" that failed.... no more than 10% or 20% of agents tried in mice succeed (Golden, Time, 151: 44, see first paragraph)." Gura (1997, Science, 278: 1041-1042, see page 1041, 1st col., 3rd parag.) teaches that pharmaceutical companies often test candidate drugs in animals carrying transplanted human tumors, in a model called a xenograft. Gura teaches that only very few drugs that showed anticancer activity in xenografts made it to the clinics and many studies show that xenograft models miss effective drugs. Gura teaches that animal models do not handle drugs the same way a human body does. Gura also point out that using human cells in culture may be one way of identifying possible candidate drugs, one pitfall of using cultured cells is that there is no indication that the drug will make it to the target site. Finally, at the time of filing, the art teaches an example wherein a p53 –null pancreatic carcinoma cell (AsPC-1) was transduced with a vector comprising a nucleic acid sequence encoding p53 (Kimura et al., 1997, Anticancer Research, 17(2A): 879-883, abstract). Kimura et al. teach that the p53 expressed in the carcinoma cells was active, as p21WAF1/CIP1 protein was induced. However, cell growth of the transduced cells was similar to the parent cells and growth of the transduced cells when inoculated into nude mice remained the same as untransduced cells. Further, in vitro studies testing the sensitivity of the cells to 4 different anticancer drugs demonstrated that the cells,

transduced with the p53 vector were not sensitive to the anticancer agents. The study by Kimura et al. thus demonstrates that the claims are not enabled for its full scope. Thus, while the specification teaches treatment of cisplatin, doxorubicin, or 5-Fluorouracil and p53Ad vector on SCID mice comprising xenotransplants of SK-OV-3, DU-145, MDA-MB-468, and SCC-15 cancer cell lines, the specification does not overcome the unpredictability taught by the art such that the scope of the claims can encompass the use of any microtubule affecting agent, in any mammalian cancer cell, in any mammal.

Thus, the specification, while being enabling for:

1) an *in vitro* method of treating mammalian cancer cells deficient in functional p53, said method comprising contacting said cancer cells with a nucleic acid encoding p53 and also contacting said cancer cells with a microtubule affecting agent, such that one or more disease characteristic of the cancer cell is ameliorated, wherein the mammalian cancer cells are human head and neck, ovarian, prostate, or mammary cancer cells,

2) an *in vivo* method of treating mammalian cancer cells deficient in functional p53, said method comprising injecting intratumorally said cancer cells with a nucleic acid encoding p53 and also contacting said cancer cells with a microtubule affecting agent, such that one or more disease characteristic of the cancer cell is ameliorated, wherein the mammalian cancer cells are human head and neck, ovarian, prostate or mammary cancer cells,

does not reasonably provide enablement for:

an *in vivo* method of treating mammalian cancer cells deficient in functional p53, said method comprising any route of administration of a nucleic acid encoding p53, other than intratumoral, to said cancer cells, and contacting said cancer cells with a microtubule affecting agent, such that one or more disease characteristic of the cancer cell is ameliorated, wherein the mammalian cancer cells are human head and neck, ovarian, prostate, or mammary cancer cells.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-5, 9-22, 25-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 uses the phrase, "contacting cells from said cancer cells (line 2)." This is unclear as it implies that that there is one subset of cancer cells which will be treated with a nucleic acid encoding p53 and another subset of cancer cells that are not treated. Subsequently, in line 3, the phrase, "also contacting said cells with a microtubule affecting agent," is unclear as the antecedent basis is unclear. The phrase, "contacting cells from said cancer cells," may be written as,

"contacting said cancer cells." The Applicant is required to ensure that no new matter has been added by such an amendment.

Claim 4 is unclear. Claim 4 uses the phrase, "contacting a cell with a chemotherapeutic agent." "A cell" appears to be any other type of cell, other than the ones described in claim 1.

Claims 20-22 are unclear because they recite the phrase, "said cells," which refers back to claim 3, when then refers back to claim 1. Because of the phrasing, "contacting cells from said cancer cells, " in claim 1, it is unclear which cells "said cells" is referring.

Claim 3 is indefinite due to the recitation, "paclitaxel derivative." One skilled in the art would not know the metes and bounds of the term "paclitaxel derivative" because the specification has not defined the range of variations in structure that would still constitute a compound as a "derivative" of paclitaxes. Due to the indefinite nature of the term "paclitaxel derivative," one skilled in the art would not know what methods would be embraced by claim 3.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 9, 10, 20, 79 are rejected under 35 U.S.C. 102(b) as being anticipated by Blagosklonny and El-Deiry (1996, Int. J. Cancer, 67: 386-392, see IDS submitted March 11, 2004, reference AC).

Claim 1 is directed to a method of treating mammalian cancer cells deficient in functional p53, wherein a nucleic acid construct comprising a nucleic acid sequence encoding p53 and a microtubule affecting agent is contacted with said cancer cells, such that one or more disease characteristic of the cancer cell is ameliorated, and wherein the cancer cell are human head and neck, ovarian, prostate, or mammary cancer cells. Claim 3 narrows claim 1 wherein the microtubule affecting agent is paclitaxel or a paclitaxel derivative. Claim 9 narrows claim 1, wherein the nucleic acid is delivered by a vector, including a viral vector, and a recombinant adenoviral vector. Claim 10 narrows claim 1, wherein the nucleic acid is delivered by a recombinant adenoviral vector. Claim 20 narrows claim 3, wherein the cancer cells are first contacted with a nucleic acid encoding p53 and then is contacted with paclitaxel or a paclitaxel derivative. Claim 79 is to a method of treating human head and neck, ovarian, prostate, or mammary cells *in vitro*, wherein cancer cells are contacted with a nucleic acid sequence encoding a p53 tumor suppressor protein and a microtubule affecting agent, such that one or more disease characteristics of the cancer cell is ameliorated.

Blagosklonny and El-Diery teach that cancer cells were obtained from a variety of human tissues (e.g.: breast, ovarian, prostate). Some of the cancer cells were comprised of functional endogenous p53 and others had mutations in p53, or were comprised of a deletion in p53 (Balgosklonny and El-Diery, page 388, Table 1). Balgosklonny and El-Diery teach that some breast cancer cells (MCF7 and SKBr3) were examined to determine if there could be a synergistic

effect between administration of an adenoviral construct comprising p53 and cytotoxic agents. Balgosklonny and El-Diery teach that both cell lines were treated with adenovirus and then drugs, such as mitomycin C, adriamycin, or vincristine, were added to the media 8 hours later (Balgsklonny and El-Diery, see Figure 5 legend). While there appeared to be a drastic reduction in the number of cells treated with adenovirus-p53 and mitomycin C or adriamycin, there was no additional sensitivity of cells when treated with adenovirus-p53 and vincrisine (Balgsklonny and El-Diery, page 390-391, see section heading "Synergy between Ad-p53 and other cytotoxic agents," see also Figure 5).

Thus, Balgosklonny and El-Diery anticipate claims 1, 3, 9, 10, 20, 79.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-5, 9-22, 25-40, 78, 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalchman et al. (1996, J. of Immunol., 156: 1101-1109, see IDS filed March 11, 2004), in view of Gallardo et al. (1996, Cancer Research, 56: 4891-4893, see IDS filed March 11, 2004) or Fujiwara et al. (1994, Cancer Research 54: 2287-2291, see IDS filed March 11, 2004), further in view of Mujoo et al. (1996, Oncogene, 12:1617-1623).

Claims 1, 3-5, 9-22, 25-40, 78, 79 are drawn to methods of treatment of cancer cells, hyperproliferative cells or metastatic cell, wherein said cells are contacted with a tumor suppressor protein or nucleic acid and a microtubule affecting agent. Specific embodiments of said methods include wherein the tumor suppressor is p53, and wherein said proteins are delivered via an adenoviral vector, and wherein the microtubule affecting agent is paclitaxel. Other specific embodiements include the added step of contacting cells with a chemotherapeutic agent, including cisplatin, carboplatin, or navelbine.

Kalechman et al. teach treating lung adenocarcinoma cells (M109), *in vitro*, with paclitaxel (Taxol) and AS101. Kalechman et al. teach that treatment of said cells with AS101 increases protein expression of wild type p53 in a dose depend manner (Kalechman et al., page 1105, 1st col. under, "Expression of p53 protein in AS101-treated M109 cells"). This increase in p53 expression in cancer cells is important, as Kalechman et al. teach that p53 is required for efficient activation of the cell death program triggered by radiation or chemotherapeutic drugs. Furthermore, the absence of wild type p53 expression leads to a dramatic increase in cellular resistance to these agents (Kalechman et al, page 1107, 2nd col., 3rd parag., lines 11-16). While Kalechman et al. teach that increased expression of p53 would enhance cancer cell sensitivity to cancer drugs, they do not teach contacting cells with a nucleic acid encoding p53.

Gallardo et al. teach *in vitro* and *in vivo* treatment of SK-OV-3 human ovarian adenocarcinoma cells. These cells are comprised of a homozygous deletion of the p53 gene (Gallardo et al., page 4891, 1st col, 1st parag., of "Cell

Lines and Virus Preparation"). Gallardo et al. teach an adenoviral vector, in which the E1A and most of the E1B were deleted, and the vector was nonreplicative. The viral vector construct was comprised of a nucleic acid sequence encoding wild type p53 and was operably linked to a cytomegalovirus promoter (Gallardo et al., page 4891, 1st col, 2nd parag., of "Cell Lines and Virus Preparation"). Gallardo et al. teach that SK-OV-3 cells infected with AdVp53 grew more slowly than cells infected with AdVluc (adenovirus comprising a luciferase reporter gene) and mock-infected cells (Gallardo et al., page 4892, paragraph under "p53 Expression Reduces the Growth Rate of SK-V-3 Cells"). Gallardo et al. then teach the effect of combination therapy wherein cells treated with AdVp53 and radiation resulted in more cell death in cells treated with AdVp53 alone (Gallardo et al. page 4892, 2nd col., under "p53 Increases the *In Vitro* Radiation Sensitivity of SK-OV-3 Cells"). Gallardo et al. teach that SK-OV-3 tumors were grown in SCID mice until they attained a size of 0.5-0.6 cm in diameter. Tumors were then injected intratumorally with AdVp53 or AdVluc. While tumors injected with AdVp53 grew more slowly, long-term tumor control was not attained. However, tumors injected with AdVp53 and treated with radiation demonstrated tumor regression and long-term tumor cure in 45% of mice (Gallardo et al., page 2892, 2nd col., paragraph under "p53 Increases the *in vivo* Radiation Sensitivity of SK-OV-3 Tumors).

Fujiwara et al. teach *in vitro* and *in vivo* studies wherein non-small cell lung cancer cell line (H358), comprising a deletion of p53, were treated with a combination of Ad-p53 (adenovirus comprising p53) and a chemotherapy drug,

CDDP (cisplatin). In the *in vitro* study, Fujiwara et al. teach that H358 spheroids infected with CDDP and Ad-p53 were smaller in size than the spheroids from the parental line, treated only with CDDP and spheroids infected with Ad-luc (adenovirus comprising a luciferase reporter construct) treated with CDDP. Fujiwara teach that the surface of the spheroids infected with Ad-p53 were comprised of cells undergoing apoptosis (as evidenced by TUNEL staining) (Fujiwara, et al., page 2288, 1st col., 4th parag). In order to determine the efficacy of the combination treatment *in vivo*, Fujiwara et al. teach that treatment of H358 implated s.c. into nude mice with either i.p administration of CDDP or intratumoral injection of Ad-p53 showed modest slowing of growth. Tumors that received both treatments partially regressed, and the tumor size remained statistically significantly smaller than the single treatments (Fujiwara et al., page 2288, 2nd col., 2nd parag., to page 2289, 1st col., 1st parag.). In addition to the combination treatment, Fujiwara et al. teach that the growth inhibitory effect was even more pronounced after two treatment cycles (Fujiwara, et al., page 2289, 1st col., 1st parag.).

Mujoo et al., teach a study in which the p53 adenoviral construct (ACN53) was tested for efficacy in *in vitro* and *in vivo* nude mice xenografts. Mujoo et al. teach that the transduction efficiency of adenovirus is high, wherein more than 98% of the cells expressed a beta-galactosidase reporter gene when infected with an adenovirus comprising lacZ (Mujoo et al., page 1618, 1st col. under "Examination of *in vitro* Transduction"). In the *in vitro* study, SK-OV-3 (ovarian cancer cell line in which p53 is missing) infected with ACN53 was tested for its

ability to form colonies. Mujoo et al. teach that SK-OV-3 infected with ACN53 formed fewer colonies than cells infected with empty vector (Mujoo et al., page 1618, 1st col., under "Effect of ACN53 on the colony-forming ability of SK-OV-3 cells, see also Table 1). Cells infected with ACN53 also exhibited growth inhibition (Mujoo, et al., page 1619, 1st col., 1st parag.). In the *in vivo* experiment, Mujoo et al. teach that nude mice injected with SK-OV-3 cells either received treatment of 1% sucrose in PBS, ACN (empty vector), or ACN53. While Mujoo et al. teach that all mice that received PBS or empty vector died by day 45, one mouse that received ACN53 treatment survived to day 66 and another survived to day 120 (Mujoo et al., page 1620, 1st col., 1st parag.).

At the time of filing, the art teaches that the ACN53 construct is a recombinant, replication-defective, adenovirus derived from adenovirus serotype 5 (Ad5), subgroup C. The adenoviral E1a, E1b and protein IX coding regions are deleted and replaced with the p53 expression cassette. The virus is additionally deleted for 1.9 kb of DNA sequence in Early Region 3, including that sequence encoding the gp19K protein. The p53 expression cassette contains the human cytomegalovirus immediate early promoter-enhancer, the adenovirus type 2 tripartite leader sequence and a sequence encoding wild-type p53 protein. This information was obtained from the GeMCRIS-Gene Transfer Protocol Reports site (the Examiner used the words, "ACS53," and "protein IX" as the key words in Google; upon opening the page, the "scientific abstract" link provides information regarding the ACS53 vector). While no information regarding whether ACS53 comprised a deletion in adenovirus early region 4 (claim 14), the art teaches

adenoviral vectors comprising a deletion in early region 4 (e.g. see Zhang, Expert Opinion on Investigational Drugs, 1997, 6: 1419-1457, see page 1439, 2nd col., "Partial E4 deletion vectors"). An artisan of ordinary skill could take the teachings of Zhang and implement them to generate a vector comprising a deletion of E4.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to express exogenous p53 in tumor cell lines that do not express endogenous p53, in order to obtain cancer cells that are primed for effective activation of the cell death program triggered by radiation or chemotherapeutic drugs, as taught by Kalechman et al. The idea of combination therapy is supported by reduction to practice in the studies taught by Gallardo et al. and Fujiwara et al.

Further, it would have been obvious to one of ordinary skill in the art to additionally treat tumor cells with additional chemotherapeutic agents, in addition to the combination of two treatments. Even if the effects are additive (versus synergistic), using two treatment methods would be better than one treatment methods. It thus follows that using three treatments, as described in the instant application, would be better than using one or two treatment methods. One would have been motivated to treat cells with three treatments, particularly if the three treatments have different mechanisms of action, like Taxol, cisplatin, and p53.

Further, it would have been obvious to one of ordinary skill in the art to treat cancer cells, hyperproliferative cells and metastatic cells using a variety of doses, varying the order of contact by the agents, administering through different

routes, and using different dosage cycles, as claimed, because the limitations claimed are all within the range of typical experimental parameters.

One having ordinary skill in the art would have been motivated to use an adenoviral vector comprising a nucleic acid encoding p53, as a way of introducing p53 protein into cancer cells, as taught by Gallardo et al and Fujiwara et al. Mujoo et al. teach a modified adenoviral vector comprising a nucleic acid sequence encoding p53 and also teach that the adenoviral vector used in their studies transduced cancer cells at high efficiency. Motivation to treat cancer in a combination therapy was provided by the teachings of Gallardo et al., and Fujiwara et al, who teach that combination therapy would be one way of ameliorating disease characteristics of cancer cells. There would have been a reasonable expectation of success given the results of Kalechman et al. for teaching that cancer cells that do not express functional p53 are more susceptible to cancer treatment when treated with exogenous p53, Gallardo et al. and Fujiwara et al. who teach that combination therapy was more effective at reducing disease characteristics of cancer cells than therapy in which one cancer treatment was used, and Mojoo et al. for teaching a modified adenoviral vector that expresses p53.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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